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NEURODEGENERATIVE DISEASE

Harnessing virus-mediated mitochondrial protection to combat neurodegeneration

Recent studies have highlighted the role of mitochondrial dysfunction in several neurodegenerative diseases. Now, a study in rat models of Parkinson's disease highlights the therapeutic benefit of protecting mitochondrial complex I activity with a viral non-coding RNA delivered to the brain using a peptide derived from the rabies virus glycoprotein (RVG). This novel therapeutic strategy could have important implications for the treatment of Parkinson's disease and other neurodegenerative diseases involving impaired mitochondrial function.

The non-coding p137 RNA, derived from the human cytomegaloviral β2.7 transcript, is expressed during viral infection. It interacts directly with mitochondrial complex I and seems to be essential for preventing cell death and maintaining energy production in infected cells. In this study, Sinclair and colleagues set out to investigate whether p137 RNA could prevent the loss of dopaminergic neurons in experimental models of Parkinson's disease.

To deliver the RNA to the brain, the authors used a previously described RVG derivative containing nine arginine residues that facilitate RNA binding: RVG9R. This peptide binds to acetylcholine receptors, which are exclusively expressed in central nervous system cells, and has been shown to deliver small interfering RNA to the brain following peripheral administration, thus overcoming the need to use more invasive intracerebral delivery procedures.

First, the authors showed that the p137 RNA–RVG9R complex protected cells cultured *in vitro* from exposure to rotenone, a mitochondrial complex I inhibitor, and 6-hydroxydopamine (6-OHDA), a neurotoxin that selectively kills dopaminergic neurons and is commonly used to induce Parkinson's-like disease in laboratory animals. In light of these results, they administered the complex via intravenous injection to rats 3 days before an acute intranigral 6-OHDA insult. Such pretreatment significantly attenuated the functional deficits induced by the lesion, as assessed in several behavioural tests.

Further experiments showed that in rats treated with p137 RNA–RVG9R, p137 physically interacts with mitochondrial complex I and protects its enzymatic activity in the nigral tissue following the 6-OHDA insult. Importantly, repeated p137 RNA–RVG9R treatment 1–2 days after an intrastriatal 6-OHDA injection was able to attenuate the loss of dopaminergic neurons in the substantia nigra and correct the behavioural deficits induced by the lesion without stimulating a host immune reaction. The therapeutic complex failed to elicit an increase in T cell infiltration, microglial activation or an antibody response, indicating that the treatment is non-immunogenic.

Although future work should assess the effects of p137 RNA–RVG9R in transgenic models of Parkinson's disease and determine the pharmacokinetic profile of the agent, this study supports the idea that mitochondrial dysfunction is at the heart of this neurodegenerative disorder and that a non-coding viral RNA could be an efficient and feasible approach to protect these organelles from damage. Moreover, the use of another virus-derived peptide to deliver the RNA transvascularly to damaged neurons could be useful for future clinical applications.

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ORIGINAL RESEARCH PAPER Kuan, W. L. *et al.* A novel neuroprotective therapy for Parkinson's disease using a viral noncoding RNA that protects mitochondrial Complex I activity. *J. Exp. Med.* **209**, 1–10 (2012)